Remarks

I. Rejection of Claims 22-24 and 26-28 under 35 U.S.C. §112, Second Paragraph.

The Examiner rejected claims 22-24 and 26-28 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In the Advisory action the Examiner stated the following:

> The proposed amendment to claims 22-24 and 26-28 filed 6/20/2005 is acknowledged. It is noted that the proposed amendment would overcome the 112, 2nd paragraph rejection. However, the proposed amendment will not be entered because the amendment would add limitations that are not currently presented in claims 22-24 and 26-28. Since the new limitations are not currently presented in the pending claims, additional search and/or consideration would be required with respect to the new limitations. (Advisory action, dated 25 July 2005, page 2, first paragraph.)

In view of the amendments presented in applicants' Response to Final Rejection and Amendment, dated 20 June 2005, and the Examiner's comments in the Advisory action, applicants submit that the boundaries of the claims are capable of being understood by one of ordinary skill in the art. Therefore, applicants respectfully request that the rejection of the claims under 35 U.S.C. §112, second paragraph, be withdrawn.

II. Addressing the Examiner's Rejection of Claims 1-20 under 35 U.S.C. §112, First Paragraph.

In the Advisory action, dated 25 July 2005, the Examiner maintained the rejection of claims 1-20 under 35 U.S.C. §112, first paragraph, asserting "the instant claims are enabled for a method of reducing the size of a tumor by intratumoral injection of the Ad5 vector disclosed as dl922/947, dl1107 or pm 928, but not for the full scope encompassed by the claims." (Advisory action, dated 25 July 2005, page 2, paragraph 2). By this amendment, applicants have canceled claims 1-5, 14, and 16 and added new claims 29-34. The newly added claims are dependent on either claim 12 or claim 15. The following arguments regarding the scope of enablement apply to all still-pending claims embraced by the Examiner's previous rejection of claims 1-20 (i.e., 6-13, 15, 17-20), as well as newly presented claims 29-34.

Applicants thank the Examiner for the Examiner's clarification of the rejection of

claims 1-20 under 35 U.S.C. §112, first paragraph, which the Examiner set forth in the Advisory action, dated 25 July 2005. In view of the Examiner's clarification, applicants submit that there are essentially two remaining scope of enablement issues. The first, asserted scope of enablement issue relates to use of the disclosed adenoviral mutants in the practice of the methods of the present invention. The Examiner stated that applicants have fully enabled how to make the adenoviral mutants of the method claims of the present invention:

> Thus, the Examiner has indicated that the claims are broad with respect to the mutant adeoviruses (*sic*) encompassed by the claims and that **the specification, although it has provided guidance for making the mutant adenoviruses,** the mutant viruses may not have the same function. (Advisory action, dated 25 July 2005, page 2, paragraph 2, emphasis added.)

Accordingly, the first, asserted scope of enablement issue relates to applicants use of the described mutants in the methods of the present invention.

The second, asserted scope of enablement issue relates to "a lack of enablement for in vivo embodiments by any route of administration other than direct intratumoral delivery" (Advisory action, dated 25 July 2005, page 2, second paragraph).

Applicants submit that the Examiner has, for both of the above scope issues, failed to establish a *prima facie* case for lack of enablement commensurate in scope with these claims. Applicants' reasoning to support this failure is set forth below. However, first applicants set forth the reasons that the specification provides enablement commensurate in scope with the claimed subject matter.

A. Applicants Submit the Specification Provides Enablement Commensurate in Scope with the Claimed Subject Matter.

(i) The Examiners Assertions Regarding Use of Mutants Other Than dl922/947, dl1107 or pm 928 in the Methods of the Present Invention.

The first, asserted scope of enablement issue relates to use of the disclosed adenoviral mutants in the practice of the methods of the present invention.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). A patent may be enabling even though some experimentation is necessary.

United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217 (Fed. Cir. 1988). Further, a considerable amount of routine experimentation is permissible if the specification provides a reasonable amount of guidance, with respect to the direction in which experimentation should proceed, to enable the determination of how to practice a desired embodiment of the claimed invention. *See, e.g., Ex parte Forman*, 230 USPQ 546, 547 (PTO Bd. Pat. App. & Int'f 1986); *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

Applicants have clearly enabled one of ordinary skill in the art to use the present invention without undue experimentation. Applicants have explicitly set forth the value of E1A-CR2 RB binding site mutant adenoviruses (see, for example, specification page12, lines 10-15 and 29-32). Applicants explicitly set forth *in vitro* and *in vivo* examples of the use of deletion mutants and a missense mutant in the E1A-CR2 region of adenovirus in the methods of the present invention (see, for example, specification pages 9-12 and Examples 1-6). Accordingly, there is no basis for a limitation of applicants' invention to three particular mutant constructs as asserted by the Examiner (that is, "the instant claims are enabled for a method of reducing the size of a tumor by intratumoral injection of the Ad5 vector disclosed as dl922/947, dl1107 or pm 928, but not for the full scope encompassed by the claims." (Advisory action, dated 25 July 2005, page 2, paragraph 2)).

The following summary serves to further illustrate that the present specification enables one of ordinary skill in the art to use the claimed invention without undue experimentation. There are three independent method claims pending in the present application, that is, claims 11, 12 and 15. All three method claims at least comprise a limitation relating to substantial and selective killing of endothelial cells compared to quiescent endothelial cells, for example, as follows:

> 11. In a cell population comprising dividing and quiescent endothelial cells, **a method for killing said dividing endothelial cells with substantially less killing of said quiescent endothelial cells**, said method comprising contacting said cell population under infective conditions with a replication competent adenovirus, said adenovirus comprising a mutation in an E1A CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said cell population, wherein said mutant adenovirus replicates to higher titers in said dividing cells than wild type adenovirus.
>
> 12. **A method for substantially and selectively killing dividing endothelial cells and cancer cells compared to quiescent endothelial cells in a cell population comprising said three cell types**, said method

comprising contacting said cell population under infective conditions with a replication competent adenovirus comprising a mutation in an E1A-CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said cell population.

15. A method for controlling angiogenesis in an animal by **substantially and selectively killing dividing microvascular endothelial cells compared to quiescent microvascular endothelial cells**, said method comprising administering to said animal in need of said control a replication competent adenovirus comprising a mutation in an E1A-CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said microvascular endothelial cells. (Claims as presently amended, emphasis added.)

Applicants submit that the specification enables one of ordinary skill in the art to use the methods of the present invention relating to substantial and selective killing of endothelial cells compared to quiescent endothelial cells, as well as greater cytopathogenicity relative to wild-type adenovirus of the mutant adenoviruses of the present invention in cancer cells and proliferating endothelial cells, without undue experimentation. In the specification, applicants' correlate mutations in a specific genetic region of adenovirus to the observed desirable phenotype (e.g., substantial and selective killing of endothelial cells compared to quiescent endothelial cells, as well as greater cytopathogenicity relative to wild-type adenovirus of the mutant adenoviruses of the present invention in cancer cells and proliferating endothelial cells). This is essentially a classic genetic analysis to associate a mutation in a particular genetic region with an observed phenotype. Applicants associate the desirable phenotype with mutation of the E1A-CR2 region of adenovirus. Briefly, applicants carried out this analysis as follows.

Applicants demonstrated the cytopathic effect (CPE) of adenoviral E1A-CR2 RB family member binding mutants against a number of tumor cell types relative to wild-type adenovirus (see, for example, Example 1, page 16, line 31, to page 17, line 4). Further, applicants demonstrated that the three mutants tested (that is, two deletion mutants each having different deletions in the E1A-CR2 region of adenovirus and one missense mutant having a mutation in the E1A-CR2 region of adenovirus) showed substantial and selective killing of endothelial cells compared to quiescent endothelial cells (see, for example, specification page 17, lines 10-12). Applicants further demonstrated that the adenoviral E1A-CR2 RB family member binding mutants replicated better than wild-type adenovirus in

proliferating endothelial cells and in human tumor cells (see, for example, specification page 17, line 22, to page 18, line 10). These data support the present invention as set forth by the applicants:

> Thus, taken together the preferred embodiment of the invention is adenoviral E1A RB family member binding mutants, and **more preferred are adenoviral E1A-CR2 RB family member mutants**, that are mutated in the RB family member binding region of E1A. These viruses show **reduced replication in quiescent normal cells, while replication and cytopathogenicity is greater than wild-type adenovirus in cancer cells and proliferating endothelial cells.** (Specification, page 12, lines 10-15, emphasis added.)

These data illustrate two desirable phenotypes of the adenoviral E1A-CR2 RB family member binding mutants of the present invention (that is, (a) reduced replication in quiescent normal cells, while (b) replication and cytopathogenicity is greater than wild-type adenovirus in cancer cells and proliferating endothelial cells). In addition, two of the adenoviral E1A-CR2 RB family member binding mutants (one of the deletion mutants and the missense mutant) were used by applicants to demonstrate efficacy against tumors *in vivo* using human tumor xenografts in athymic mice (see, for example, specification page 11, lines 17-26, and page 18, line 11, to page 19, line 14) -- these data support that the phenotypes of applicants' mutants seen *in vitro* correlate to *in vivo* activity. Further, one of the adenoviral E1A-CR2 RB family member binding mutants (a deletion) was used by applicants to demonstrate decreased replication and toxicity *in vivo* in quiescent cotton rat lung cells relative to wild-type adenovirus (see, for example, specification page 11, lines 17-26, and page 19, line 15, to page 20, line 7) -- these data also support that the phenotypes of applicants' mutants seen *in vitro* correlate to *in vivo* activity.

Thus applicants identified the genetic region of the E1A-CR2 region of adenovirus as a valuable target for mutations to produce adenoviral mutants having a desirable phenotype (e.g., substantial and selective killing of endothelial cells compared to quiescent endothelial cells, as well as greater cytopathogenicity relative to wild-type adenovirus of the mutant adenoviruses of the present invention in cancer cells and proliferating endothelial cells). Again, the method of mutation mapping is a standard genetic analysis to establish structure/function relationships. Applicants have established the structure/function relationship of mutations in the E1A-CR2 region of adenovirus / substantial and selective

killing of endothelial cells compared to quiescent endothelial cells, as well as greater cytopathogenicity relative to wild-type adenovirus of the mutant adenoviruses of the present invention in cancer cells and proliferating endothelial cells.

In view of the teachings of applicants of this structure/function relationship, one of ordinary skill in the art may now use the adenoviral E1A-CR2 RB family member binding mutants of the present invention in the methods of the present invention. Even if, for the sake of argument, some experimentation is required, a considerable amount of routine experimentation is permissible if the specification provides a reasonable amount of guidance, with respect to the direction in which experimentation should proceed, to enable the determination of how to practice a desired embodiment of the claimed invention. *See, e.g., Ex parte Forman*, 230 USPQ 546, 547 (PTO Bd. Pat. App. & Int'f 1986); *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Accordingly, applicants have clearly enabled one of ordinary skill in the art to make and use the entire scope of adenoviral E1A-CR2 RB family member binding mutants in the methods of the present invention without undue experimentation, well beyond the Examiner's asserted scope of "the Ad5 vector disclosed as dl922/947, dl1107 or pm 928, but not for the full scope encompassed by the claims" (Advisory action, dated 25 July 2005, page 2, paragraph 2).

(ii) The Examiners Assertions Regarding a Lack of Enablement for In Vivo Embodiments by Any Route of Administration Other than Direct Intratumoral Delivery.

The second, asserted scope of enablement issue relates to "a lack of enablement for in vivo embodiments by any route of administration other than direct intratumoral delivery" (Advisory action, dated 25 July 2005, page 2, second paragraph).

As discussed herein above, applicants have demonstrated the *in vivo* efficacy of the methods of the present invention using intratumoral injection of adenoviral E1A-CR2 RB family member binding mutants of the present invention. Further, applicants have demonstrated, by use of intranasal inoculation, that the adenoviral E1A-CR2 RB family member binding mutants of the present invention show decreased replication and toxicity in quiescent cotton rat lung cells compared to wild-type adenovirus (see, for example, specification, page 11, line 27, to page 12, line 15, and page 19, line 15, to page 20, line 7). Further, applicants have taught a variety of formulations and methods of administration for

the adenoviral E1A-CR2 RB family member binding mutants for use in the methods the present invention (see, for example, specification, pages 13-15).

Moreover, Applicants have incorporated by reference U. S. Patent No. 5,677,178 in its entirety (see, for example, specification, page 14, lines 19-21, and page 5, lines 4-6). Column 17, lines 1-20, of U. S. Patent No. 5,677,178 states the following:

> A adenovirus suspension containing about 10.sup.3 to 10.sup.12 or more virion particles per ml may be inhaled as a mist (e.g., for pulmonary delivery to treat bronchogenic carcinoma, small-cell lung carcinoma, non-small cell lung carcinoma, lung adenocarcinoma, or laryngeal cancer) or swabbed directly on a tumor site for treating a tumor (e.g., bronchogenic carcinoma, nasopharyngeal carcinoma, laryngeal carcinoma, cervical carcinoma) or may be administered by infusion (e.g., into the peritoneal cavity for treating ovarian cancer, into the portal vein for treating hepatocarcinoma or liver metastases from other non-hepatic primary tumors) or other suitable route, including direct injection into a tumor mass (e.g., a breast tumor), enema (e.g., colon cancer), or catheter (e.g., bladdercancer).

This teaching of U. S. Patent No. 5,677,178 illustrates a number of suitable routes of administration of adenoviral compositions in addition to intratumoral injection. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). A patent may be enabling even though some experimentation is necessary. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217 (Fed. Cir. 1988).

Applicants' specification allows one reasonably skilled in the art to "make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." Not every species encompassed by the claims, even in an unpredictable area like the chemical sciences, needs to be disclosed. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). As discussed herein above, two of the adenoviral E1A-CR2 RB family member binding mutants (one of the deletion mutants and the missense mutant) were used by applicants to demonstrate efficacy against tumors *in vivo* using human tumor xenografts in athymic mice (see, for example, specification page 11, lines 17-26, and page 18, line 11, to page 19, line 14) -- these data support that the phenotypes of applicants' mutants seen *in vitro* correlate to *in vivo* activity. Further, one of the adenoviral

E1A-CR2 RB family member binding mutants (a deletion) was used by applicants to demonstrate decreased replication and toxicity *in vivo* in quiescent cotton rat lung cells relative to wild-type adenovirus (see, for example, specification page 11, lines 17-26, and page 19, line 15, to page 20, line 7) -- these data support that the phenotypes of applicants' mutants seen *in vitro* correlate to *in vivo* activity.

Finally, even if, for the sake of argument, some further experimentation is necessary for delivery methods for use in the methods of the present invention, so long as the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed, a considerable amount of routine experimentation is permissible. See, e.g., *Ex parte Forman*, 230 USPQ 546, 547 (PTO Bd. Pat. App. & Int'f 1986); *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). As noted above, the present specification and information know in the art describe a variety of routes of administration for administration of adenoviral mutants.

In view of the above amendments and arguments, applicants submit that claims 6-13, 15, 17-20, and 29-34 comply with the requirements of 35 U.S.C. §112, first paragraph. Accordingly, withdrawal of the rejection is respectfully requested.

B. The Examiner Has Failed to Establish a *Prima Facie* Case of Lack of Enablement Commensurate in Scope with the Claimed Subject Matter.

(i) The Examiners Assertions Regarding Use of Mutants Other Than dl922/947, dl1107 or pm 928 in the Methods of the Present Invention.

To support the rejection of claims 1-20 for lack of enablement commensurate in scope with the claimed subject matter, the Examiner stated the following:

> Furthermore, the Office action dated 9/15/00 also indicates reasons why the claims are only enabled for the specific indicated adenoviruses (e.g., see last paragraph of page 5). Specifically, the Examiner indicated that, "The specification lacks guidance to the breadth of the claims regarding the mutant adenovirus of the instant (*sic*), and its ultimate functioning in an in vivo method of (a) substantially and selectively killing dividing cells... The specification gives guidance for the construction of said mutants, but the claims encompass any in vivo administration of said mutant, which may not necessarily reflect similar functioning..." Thus, the Examiner has indicated that the claims are broad with respect to the mutant adeoviruses (*sic*) encompassed by the claims and that the specification, although it has provided

> guidance for making the mutant adenoviruses, the mutant viruses may not have the same function. (Advisory action, dated 25 July 2005, page 2, paragraph 2.)

However, the asserted objections to the scope enablement for the use of mutants other than dl922/947, dl1107 or pm 928 in the methods of the present invention are only unsubstantiated assertions and the previous Office actions present no evidence to support the doubts expressed by the Examiner. Whenever the PTO makes a rejection for failure to teach and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). The Examiner has presented no evidence to support the Examiner's questioning of the objective enablement by the specification of use of applicants' adenovirus comprising a mutation in an E1A-CR2 RB family member binding region of the adenovirus in the methods of the claims. However, applicants have established the structure/function relationship of mutations in the E1A-CR2 region of adenovirus / substantial and selective killing of endothelial cells compared to quiescent endothelial cells, as well as greater cytopathogenicity relative to wild-type adenovirus of the mutant adenoviruses of the present invention in cancer cells and proliferating endothelial cells. Applicants submit that they have set forth explicit support and enablement for the entire breadth of use of applicants' adenovirus comprising a mutation in an E1A-CR2 RB family member binding region of the adenovirus in the methods of the claims (i.e., pending claims 6-13, 15, 17-20, and 29-34).

If the Examiner wishes support the assertions of undue experimentation from personal experience, then such an assertion should be submitted in the form of an Examiner's affidavit. When a rejection is based on facts within the personal knowledge of the Examiner, the data should be stated as specifically as possible, and the reference must be supported, when called for by the applicant, by an affidavit from the Examiner (MPEP 706.02(a)). Such an affidavit is subject to contradiction or explanation by the affidavits of the applicant and other persons (37 C.F.R. 1.107).

As discussed herein above, applicants have demonstrated use of adenovirus

comprising a mutation in an E1A-CR2 RB family member binding region of the adenovirus in the methods of the claims using *in vitro* and *in vivo* experiments using three mutants having different mutations in the E1A-CR2 RB family member binding region, specifically Dl922/947, having a deletion of amino acids 122 to 129, dl1107 having a deletion of amino acids 111 to 123, and Pm928 having a point mutation resulting in conversion of amino acid 124 from a cysteine to a glycine. The Examiner has not presented any evidence to prove the Examiner's assertion that other mutants of the E1A-CR2 RB family member binding region "may not necessarily reflect similar functioning" (Advisory action, dated 25 July 2005, page 2, paragraph 2). Not every species encompassed by the claims, even in an unpredictable area like the chemical sciences, needs to be disclosed. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

In view of the above arguments, applicants submit that the Examiner has failed to establish a *prima facie* case for lack of enablement for use of mutants other than dl922/947, dl1107 or pm 928 in the methods of the present invention (corresponding to pending claims 6-13, 15, 17-20, and 29-34). Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

(ii) The Examiners Assertions Regarding a Lack of Enablement for *In Vivo* Embodiments by Any Route of Administration Other than Direct Intratumoral Delivery.

The second, asserted scope of enablement issue relates to "a lack of enablement for in vivo embodiments by any route of administration other than direct intratumoral delivery" (Advisory action, dated 25 July 2005, page 2, second paragraph).

In support of the rejection for lack of enablement commensurate in scope with the claimed subject matter, the Examiner relies on a generic discussion of alleged shortcomings of general gene delivery and gene therapy methods (see, for example, Office action, dated 15 September 2000, pages 7-8, Office action, dated 5 June 2001, pages 2-3, Office action, dated 17 January 2002, pages 2-3 "reasons of record," Office action, dated 20 April 2005, pages 2-5 "reasons of record"). The Examiner presents neither evidence nor teachings specifically concerning routes of delivery of therapeutic adenoviruses in support of the rejection. Essentially the Examiner's rejection of claims 1-20 for lack of enablement commensurate in scope with the claimed subject matter has relied, since the first rejection dated 15 September

2000, on the same two references that present general teachings regarding gene therapy -- specifically Dang, et al., and Eck, et al., and the reference of Dura, et al., that presents general teachings concerning potential shortcomings for systems for identifying new drugs. The Examiner does not point to any specific teaching in any of these references concerning the use of oncolytic adenoviruses, or adenovirus mutants, as described in the present specification, having greater cytopathogenicity relative to wild-type adenovirus in cancer cells and proliferating endothelial cells, wherein such teachings support the assertions of the Examiner.

However, applicants have previously discussed (see, for example, Response to Final Rejection and Amendment, dated 20 June 2005, page 10) specific references in the field of oncolytic adenoviruses that provide discussion of routes of delivery for adenoviral vectors. In addition to these references, the issued U.S. Patent literature comprises several examples of issued claims to oncolytic adenoviral vectors wherein the claims embrace *in vivo* uses and routes of administration in addition to direct intratumoral delivery. For example, U.S. Patent No. 5,677,178 contains the following issued method claims (emphasis added):

> 1. A method for ablating neoplastic cells in a cell population, comprising the steps of: contacting under infective conditions (1) a recombinant replication deficient adenovirus lacking an expressed viral oncoprotein capable of binding a functional p53 tumor suppressor gene product, with (2) a cell population comprising non-neoplastic cells containing said functional p53 tumor suppressor gene product which forms a bound complex with a viral oncoprotein and neoplastic cells lacking said functional p53 tumor suppressor gene product, thereby generating an infected cell population.
> 8. A method according to claim 1, wherein said cell population comprising neoplastic cells and non-neoplastic cells is present in a mammal and **said contacting step is performed in vivo by administering the recombinant replication deficient adenovirus to a mammal.**
> 9. A method according to claim 8, wherein the mammal is a human.

The specification of U.S. Patent No. 5,677,178 describes the following routes of administration:

> Suspensions of infectious adenovirus particles may be applied to neoplastic tissue by various routes, including intravenous, intraperitoneal, intramuscular, subdermal, and topical. A adenovirus suspension containing about 10.sup.3 to 10.sup.12 or more virion particles per ml may be inhaled as a mist (e.g., for pulmonary delivery to treat bronchogenic carcinoma, small-cell lung carcinoma, non-small cell lung carcinoma, lung adenocarcinoma, or laryngeal cancer) or swabbed directly on a tumor site for treating a tumor (e.g., bronchogenic carcinoma, nasopharyngeal carcinoma, laryngeal carcinoma, cervical carcinoma) or may be administered by infusion (e.g., into the peritoneal cavity for treating ovarian cancer, into the portal vein for treating

> hepatocarcinoma or liver metastases from other non-hepatic primary tumors) or other suitable route, including direct injection into a tumor mass (e.g., a breast tumor), enema (e.g., colon cancer), or catheter (e.g., bladder cancer). (U.S. Patent No. 5,677,178, col. 16, line 65, to col. 17, line 14.)

The present specification describes a variety of routes of administration for the methods of the present invention (see, discussion of enablement herein above) including reference to U.S. Patent No. 5,677,178 (see, for example, specification page 14, lines 20-21). Applicants thank the Examiner for withdrawal of the Examiner's comments directed to the scope of enablement of U.S. Patent No. 5,677,178 (Advisory action, dated 25 July 2005, page 3, first paragraph).

Whenever the PTO makes such a rejection for failure to teach and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). In view of the above-recited teachings of the literature with regard to oncolytic adenoviruses, their killing properties, and routes of administration, the "current literature as a whole" cannot be said to support the Examiner's allegations of a lack of enablement for the scope of the claimed invention.

In view of the above arguments, applicants submit that the Examiner has failed to establish a *prima facie* case for lack of enablement "for *in vivo* embodiments by any route of administration other than direct intratumoral delivery" (Advisory action, dated 25 July 2005, page 2, second paragraph) (corresponding to pending claims 6-13, 15, 17-20, and 29-34). Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

III. Rejection of Claims 1-6 Under 35 U.S.C. §102(e).

In the Advisory action, dated 25 July 2005, the Examiner maintained the rejection of claims 1-6 under 35 U.S.C. §102(e) asserting that the claims are anticipated by Bischoff, et al. (U.S. Patent No. 6,080,578).

Applicants' arguments regarding applicants' belief that the Examiner has failed to establish an anticipation rejection based on inherency are set forth in applicants' Response to

Final Rejection and Amendment, dated 20 June 2005, and applicants' Reasons For Pre-Appeal Brief Request For Review, dated 25 August 2005.

For the reasons of record, applicants maintain that the asserted rejection of claims 1-6 under 35 U.S.C. §102(e) is improper. However, in an effort to facilitate prosecution, in this paper applicants cancel claims 1-5 and amend claims 6-10 to be dependent on original claim 11. Accordingly, dependent claims 6-10 are at least distinguished over the reference of Bischoff, et al., by virtue of their dependence on original, independent, claim 11.

Accordingly, in view of the above arguments and amendments, applicants submit that the rejection of claims 1-6 under 35 U.S.C. §102(e) is moot and applicants respectfully request withdrawal of the rejection.

Conclusion

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

Gregory Giotta, Ph.D., Esq.
(Reg. No. 32,028)
ONYX Pharmaceuticals, Inc.
2100 Powell Street
Emeryville, CA 94608
Phone: (510) 597-6502
Facsimile: (510) 597-6610.

If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact Gregory Giotta at (510) 597-6502.

Respectfully submitted,

Date: 17 Jan 2006 By: Gary R Fabian

Gary R. Fabian, Ph.D.
Registration No. 33,875
Agent for Applicants